

Research Overview

Vaccination for T Cell-Mediated Neuroprotection: Dream or Reality?

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Strategy, Management and Health Policy				
Venture Capital Enabling Technology	Preclinical Research	Preclinical Development Toxicology, Formulation Drug Delivery, Pharmacokinetics	Clinical Development Phases I-III Regulatory, Quality, Manufacturing	Postmarketing Phase IV

ABSTRACT Degenerative diseases of the central nervous system (CNS) are characterized by progressive degeneration, which continues even after the primary causative factor has been identified and neutralized or removed. The progressive degeneration is thought to be a self-perpetuating process, attributable in part to factors derived from the degenerating nerves themselves. If this is so, the mediators of toxicity causing secondary degeneration in the various degenerative diseases are likely to be similar. Common mediators include excitatory amino acids, compounds that cause oxidative or metabolic stress, and factors that disturb the ionic balance of the nerve's extracellular milieu. It is proposed here, based on recent work by the author and by others on CNS trauma and autoimmunity, as well as on accumulated information about the professional role of the adaptive and the immune response in general, that active or passive T cell-mediated autoimmunity directed against self-antigens associated with the disorder will be beneficial in halting the spread of damage. *Drug Dev. Res.* 50:223–225, 2000. © 2000 Wiley-Liss, Inc.

Key words: adaptive immune response; autoimmunity; copolymer-1; neurodegenerative diseases; neuroprotection; T cells; spinal cord injury

NEURODEGENERATIVE DISEASES; SELF-PERPETUATING DEGENERATION

In individuals suffering from a neurodegenerative disease, it is conceivable that at any given time some neurons have already degenerated and died, some are actively undergoing degeneration, and some are still healthy or only marginally damaged but in the absence of therapeutic intervention will inevitably succumb to secondary degeneration [Faden et al., 1997; McIntosh, 1993; Povlishock and Christman, 1995; Yoles and Schwartz, 1998]. This progressive spread of damage is seen not only in chronic degenerative diseases but also after acute traumatic injuries to the central nervous system (CNS), where the functional outcome is often more severe than might be expected from the severity of the injury. Intensive research has therefore been devoted to the problem of progressive degeneration in an attempt to understand the underlying mechanisms and develop therapies to arrest or retard the spread of damage. Many of these studies employ animal models of acute injury to the optic nerve or spinal cord. Since the spread of damage in neuro-

degenerative diseases may be viewed as the outcome of a continuous series of acute mini-injuries, findings in the acute injury model are expected to be applicable to chronic syndromes [Schwartz et al., 1996; Schwartz and Yoles, 2000; Yoles et al., 1999].

Attempts to halt the spread of damage have included neutralizing the mediators of toxicity, inhibiting signal transduction associated with death signals, and increasing the resistance of vulnerable neurons to the injurious conditions. None of these approaches, however, makes use of the system whose chief function is to maintain and protect the organism, namely, the immune system. There are several reasons why the very system best qualified for the job has not been called upon. First, in most neurodegenerative diseases (such as Alzheimer, Parkinson, glaucoma) the active process takes place in the CNS, an immune-privileged site where any immune

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activity has long been considered harmful. Second, according to the common wisdom adaptive intervention by the immune system is needed only in cases of pathogen-associated damage. Pathogens are not involved in the spread of damage in neurodegenerative diseases. Third, some beneficial effect on the postinjury spread of damage has been obtained with antiinflammatory drugs, leading in many cases to the oversimplified conclusions related to the role of immune activities in the injured CNS [Bethea et al., 1998; Constantini and Young, 1994; Hirschberg and Schwartz, 1995; Popovich et al., 1998; Rapalino et al., 1998].

For all of the above reasons, the immune system has earned a bad reputation as a potential source of therapy in the CNS. This would explain why exploitation of adaptive immunity was, until recently, not seriously considered as a worthwhile approach in the attempt to stop the spread of damage.

DAMAGED CNS BENEFITS FROM AUTOIMMUNITY

Using rat models of partially crush-injured optic nerves and contused spinal cords, in which degeneration progresses both laterally and longitudinally, we recently observed that a well-controlled adaptive immune response is beneficial in slowing down the posttraumatic spread of damage. The immune response was mediated by T cells directed against a CNS-associated self-antigen, such as myelin basic protein (MBP) [Hauben et al., 2000a; Moalem et al., 1999], myelin oligodendrocyte protein (MOG), or proteolipid protein (PLP), or against peptides (encephalitogenic or nonencephalitogenic) derived from these proteins [Moalem et al., 1999]. T cells directed against encephalitogenic epitopes were as effective as those directed against cryptic epitopes in displaying neuroprotection, indicating that the observed neuroprotection was not related to the virulence of the autoimmune response. The response could be achieved either by active immunization with the proteins (or peptides) or by passive transfer of T cells activated by them [Hauben et al., 2000b]. On the basis of these findings, we suggested that autoimmune T cells can protect CNS neurons from the postinjury spread of damage. We further showed that the neuroprotective autoimmunity is not the result of an experimental manipulation but is an endogenous response that is awakened by the damaged neurons, although apparently not strongly-enough to be effective (Yoles et al., submitted). It thus appears that this is a physiological mechanism whereby the body attempts to cope with trauma-related nerve damage to the nervous system, but—presumably because of an evolutionary trade-off—the recruited autoimmune response, in its natural state, is neither timely nor effective [Cohen and Schwartz, 1999; Schwartz et al., 1999a,b].

The beneficial autoimmunity can, in principle, gain

access to the damaged tissue at any time, as even the healthy CNS is receptive to surveillance by T cells, which—unlike immunoglobulins or macrophages—are not restricted by the blood–brain barrier. We found that T cells which patrol the CNS accumulate preferentially at sites of injury [Moalem et al., 1999a].

The way in which the T cell-mediated immune response exerts its neuroprotective effect is not yet fully understood. Like most of the activities of adaptive immune cells, the activity is likely to be antigen-dependent. Thus, in order to exert their neuroprotective activity the T cells need to be reactivated at the site of injury. Our recent demonstration of antigen-dependent production of neurotrophic factors by T cells points to neurotrophin (NT) production as a possible facilitator of the protection provided by the T cells (Moalem et al., 2000). As a source of NTs, T cells have certain advantages over neural cells: 1) because of their mobility, T cells can be recruited to supply areas that run short of NTs due to damage; 2) the amount of NT production by T cells is determined by reactivation through signals coming from the tissue, a feature unique to immune cells; and 3) the type of NT produced may also be affected by the nature and/or intensity of the stress signals.

EXPLOITATION OF T CELL-MEDIATED AUTOIMMUNITY FOR THE TREATMENT OF DEGENERATIVE DISEASES

The finding of autoimmune neuroprotection of nerve cell bodies and fibers in the hostile environment of the injured rat spinal cord or optic nerve leads us to believe that it will prove to be a feature of other degenerative events.

Since the neuroprotective immune response found to operate under conditions of nonpathogenic damage is directed against self, it must be well controlled to avoid exceeding the risk threshold and inducing an autoimmune disease. Our studies have shown that wherever this risk exists it is outweighed by the benefit. Recently, in seeking a way to elicit a risk-free anti-self response, we found that Cop-1, a synthetic copolymer comprising the amino acids Ala, Lys, and Tyr, and known as an immunosuppressive drug, can evoke passive or active T cell-mediated immunity that is neuroprotective [Kipnis et al., 2000]. T cells specific to Cop-1, like T cells against self-antigens, were found to accumulate in the undamaged CNS. They might, therefore, represent cells that are cross-activated by CNS self-antigens in the damaged area, an activity that seems to be necessary for the expression of neuroprotective ability. Injured nerves, unlike uninjured nerves, allow the nonselective accumulation of T cells. However, only those T cells that recognize self-antigens are neuroprotective. The use of safe synthetic peptides that resemble self-antigens and T cells specific to them

are cross-activated by self-antigens and may provide a strategy for the development of safe anti-self immunity for neuroprotective purposes.

It is conceivable that the different types of damage occurring in the various neurodegenerative diseases involve different antigens, and hence that treatment might require vaccination or passive T-cell transfer associated with a disease-specific antigen. Future studies should seek to identify the specific antigen for any particular disease, the optimal timing and type of immunization (passive or active) in each case, and the most appropriate adjuvant, in order to best exploit the long-neglected immune system for the design of a physiological approach to therapy that will yield maximal benefit with minimal risk.

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